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Postoperative Inflammatory Response in Crohn's Patients: A Comparative Study

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Abstract

Background and Aims: Surgery for Crohn's disease [CD] can be complicated by an enhanced inflammatory response. This retrospective study aims to compare the inflammatory response measured by C-reactive protein [CRP] in patients operated for CD with patients undergoing similar surgery for colorectal cancer [CRC].

Methods: All CD patients undergoing an ileocaecal resection between February 2001 and December 2013 were retrieved from a prospectively maintained database. The same number of patients with a CRC of the ascending colon, undergoing a laparoscopic right hemicolectomy between March 2009 and June 2014, were retrieved from a CRC database. CRP level during the first 7 postoperative days was used as primary outcome.

Results: Totals of 112 consecutive CD patients (male 40.2%; median age: 32.3 yrs; interquartile range [IQR]: 25.2–45.1) and 112 consecutive CRC patients [male 53.6%; median age 71.6 yrs; IQR: 64.7–77.5] were included. Postoperative CRP level in the CD group was on average 27% higher compared with the CRC group [$p = 0.02$]. The day-specific differences in CRP values were 21% ($p = 0.021$, 95% confidence interval [CI]: 3% 41%), 41% [$p = 0.005$, 95% CI: 11% – 79%], 49% [$p = 0.007$, 95% CI: 11% – 96%], and 49% [$p = 0.006$, 95% CI: 12% – 100%] higher for CD patients at Days 1, 4, 5, and 6 respectively. The difference in postoperative CRP level was partially due to differences in preoperative CRP level.

Conclusion: CD patients develop a higher postoperative CRP level, probably reflecting an enhanced postoperative inflammatory response, which may be triggered by a higher preoperative inflammatory state.

Key Words: Postoperative inflammatory response; Crohn's disease; C-reactive protein; ileocaecal resection; right hemicolectomy

1. Introduction

CD is an inflammatory bowel disease with a multifactorial pathophysiology. Genetic, immune, gut microbiota, and other environmental factors play a role in the occurrence and maintenance of bowel inflammation. Unfortunately, despite the development of new drugs, about half of all CD patients will need surgery during their disease course.[1]

Patients undergoing surgery for CD appear to develop a higher inflammatory response in the postoperative phase.[2,3] This clinical presentation can mimic septic complications in the postoperative phase, leading in some cases to either imaging or second-look surgery to rule out an anastomotic leak. CD patients may react differently after surgery compared with patients undergoing similar surgical procedures for other conditions.

Most series have focused on postoperative morbidity in terms of septic complications including anastomotic leakage and the effect of immunomodulatory and biological therapy on surgical outcome.[4,5,6,7,8,9] However, the postoperative inflammatory response as such might also be affected by CD. Therefore, this study aims to compare the postoperative inflammatory response between CD patients and CRC patients undergoing either a laparoscopic ileocaecal resection or a laparoscopic right hemicolectomy, respectively.

2. Materials and Methods

All eligible patients operated for a laparoscopic ileocaecal resection for CD between February 2001 and December 2013 were retrieved from a prospectively maintained database. The same number of consecutive patients with CRC at the ascending colon undergoing a laparoscopic right hemicolectomy between March 2009 and June 2014 was retrieved from a CRC database. Only patients with elective primary laparoscopic [single or multiport] surgery were included, in order to minimise the effect of surgical access trauma on postoperative inflammatory response. Patients who needed a conversion to laparotomy were excluded for the same reason. Patients were evaluated preoperatively by cross-sectional imaging, ileocolonoscopy, or both. Patients who presented preoperatively with an intra-abdominal phlegmone or abscess, and those with documented postoperative septic complications, were excluded because of the impact of these conditions on postoperative inflammatory response. Septic complication was defined as the presence of a deep intra-abdominal abscess, an anastomotic leak, or the presence of other infectious complications [catheter sepsis, pneumonia, etc] that could influence the postoperative CRP level. Patients with CD activity at another location were excluded since inflammatory response could be influenced by that other site of inflammation. All medical charts were reviewed. The following factors were collected in the charts: gender, age at diagnosis, age at time of surgery, American Society of Anesthesiology [ASA] score, preoperative and postoperative CRP level, preoperative and postoperative medication [immunomodulatory, biological or antibiotic], and 30-day morbidity. Postoperative CRP was assessed daily as part of the routine clinical follow-up in all operated patients until discharge. Morbidity was expressed according to the Clavien-Dindo classification.[10] Antibiotics were prescribed at surgeon's discretion depending on postoperative clinical assessment.

2.1. Statistics

The primary endpoint was the difference in inflammatory response after surgery, expressed as the difference in CRP level during the first 7 postoperative days. Fisher's exact and Mann–Whitney U tests were used to compare nominal and ordinal/continuous variables between groups, respectively. Relations between ordinal/continuous variables were evaluated with Spearman correlations. General linear models for longitudinal measures using a direct likelihood approach were used to compare the evolution of CRP between both diagnosis groups during the first 7 postoperative days. A heterogeneous variance first-order autocorrelation matrix was used for the covariance structure [with robust standard errors correcting for possible misspecification of this structure]. Least-squares means and their 95% confidence intervals were plotted as a function of time. To obtain a symmetrical distribution of the model residuals, the CRP values were log-transformed, but results are presented after back-transformation to the original scale. Note that due to this transformation, the exponent of the least-squares mean can be interpreted as a geometrical mean and differences between groups on the log-scales are ratios on the original scale. In a first model, only group, time, and the interaction were considered as effects. In additional models, the comparison between both groups was made after adding potential confounders in the model. Considered confounders were age, the [log-transformed] baseline level [on the day before surgery], the use

Table 1. Clinical characteristics of patient population.

	CD patients [n = 112]	Colorectal cancer patients [n = 112]	p-Value
Gender			
Male	45 [40.2%]	60 [53.6%]	
Female	67 [59.8%]	52 [46,4%]	0.061
Median age at surgery [IQR]	32.3 [25.2 – 45.1]	71.6 [64.7 – 77.5]	< 0.001
Median preoperative CRP level [mg/dl] [IQR]	6.6 [2.8 – 17.8]	2.3 [1.0 – 4.2]	< 0.001
ASA score			
ASA <= 2	107 [95.5%]	73 [65.2%]	
ASA >= 2	5 [4.5%]	39 [34.8%]	< 0.001
Preoperative immunomodulating medication	94 [83.9%]	-	< 0.001
Anti-TNF alpha	42 [37.5%]	-	
Azathioprine	27 [24.1%]	-	
Methylprednisolone	16 [14.3%]	-	
Mesalazine	14 [12.5%]	-	
Budesonide	13 [11.6%]	-	
Methotrexate	12 [10.7%]	-	
Postoperative antibiotic therapy	27/76 [35.5%]	31/112 [27.7%]	0.264
Median postoperative length of hospital stay in days [IQR]	7.0 [6.0 – 8.0]	7.0 [6.0 – 9.0]	0.215
Postoperative morbidity score [Clavien-Dindo]			
0	93 [83.0%]	98 [87.5%]	
1	1 [0.9%]	4 [3.6%]	
2	12 [10.7%]	7 [6.3%]	
3a	1 [0.9%]	2 [1.8%]	
3b	5 [4.5%]	-	<0.001

IQR, interquartile range; CRP, C-reactive protein; ASA, American Society of Anesthesiology; TNF, tumour necrosis factor; CD, Crohn's disease.

of preoperative immunomodulating medication or antibiotics, and the use of postoperative antibiotics; *p*-values smaller than 0.05 were considered as significant. All analyses were performed using SAS software, version 9.2 of the SAS System for Windows.

3. Results

Totals of 112 CD patients [male 40.2%; median age: 32.3 yrs; IQR: 25.2 – 45.1] and 112 CRC patients [male 53.6%, median age 71.6 yrs; IQR: 64.7 – 77.5] were included. Patients' characteristics are summarised in Table 1. CRC patients were significantly older [71.6 yrs vs 32.2 yrs; $p < 0.001$], with a higher number of patients with a preoperative ASA score of more than 2 [34.8% vs 4.5%; $p < 0.001$]. Although CD patients were numerically taking postoperative antibiotics more often compared with CRC patients, this difference was not significant [35.5% vs 27.7%; $p = 0.264$]. The median duration of postoperative antibiotic therapy was longer in CD patients [5 days vs 3 days; $p = 0.009$]; 83.9% of CD patients were taking some kind of immunomodulatory or biological therapy preoperatively. Used drugs were mesalazine, azathioprine, methotrexate, methylprednisolone, budesonide, and anti-TNF alpha. No CRC patients were prescribed such medication [$p < 0.001$]. Median length of postoperative stay of both groups was similar [7 days in both groups; $p = 0.215$]. Median preoperative CRP was significantly lower in CRC patients compared with CD patients [23 mg/l vs 66 mg/l; $p < 0.001$] and in patients without any antibiotics preoperatively compared with patients under preoperative antibiotic therapy [24 mg/l vs 62 mg/l; $p < 0.001$]. Preoperative CRP was not influenced by either ASA score [$p = 0.066$] or gender [$p = 0.240$]. Patients' characteristics are listed in Table 1.

Postoperative CRP level in the CD group was on average 27% higher compared with the CRC group [$p = 0.02$]. The day-specific differences in CRP values were 21% [$p = 0.021$, 95% CI: 3% – 41%] higher in CD patients at Day 1, 41% [$p = 0.005$, 95% CI: 11% - 79%] at Day 4, 49% [$p = 0.007$, 95% CI: 11% – 96%] at Day 5 and 49% [$p = 0.006$, 95% CI: 12% - 100%] at Day 6 [Figure 1]. The magnitude of the difference between both groups remained similar after correction for age and preoperative and postoperative intake of antibiotics or immunomodulators. However, after correction for preoperative CRP level, the difference in average postoperative CRP level reduced to 14% [$p = 0.23$] in the CD group, and remained

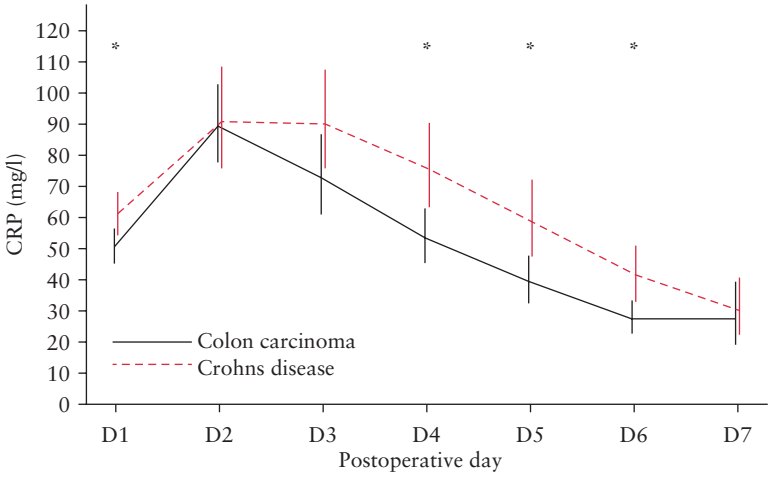

Figure 1. Postoperative (geometric) mean CRP-level with 95% confidence interval (CI) without correcting for potential confounders. Geometric mean and CI are obtained after backtransforming the results from the general linear model on the log-transformed CRP-values to the original scale. Postoperative days with a significant difference in CRP-level are indicated with * (p<0.05).

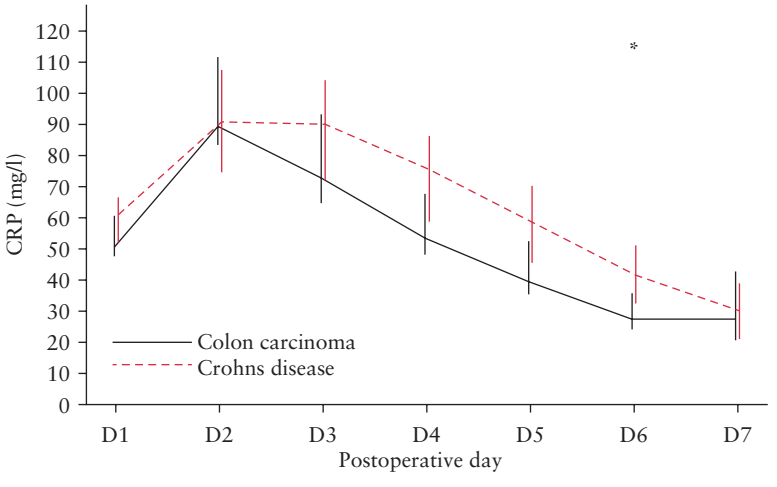

Figure 2. Postoperative (geometric) mean CRP-level with 95% confidence interval (CI), after correcting for preoperative CRP level. Geometric mean and CI are obtained after backtransforming the results from the general linear model on the log-transformed CRP-values to the original scale. Postoperative days with a significant difference in CRP-level are indicated with * (p<0.05).

Table 2. Comparison of the CRP level during first 7 postoperative days, corrected for baseline level, preoperative medication, age, and postoperative medication: parameter estimates from a general linear model for repeated measures [625 observations from 177 subjects]. The interaction reflects whether the difference between both groups depends on the time point. Note that the analysis has been performed on log-transformed measures. The exponent of the estimates reflects a ratio on the original scale.

	Estimate [SE]	*p*-Value
Day		
1	0.640 [0.132]	<0.0001
2	1.085 [0.136]	<0.0001
3	1.067 [0.148]	<0.0001
4	0.899 [0.129]	<0.0001
5	0.703 [0.117]	<0.0001
6	0.401 [0.094]	<0.0001
7	-	-
Diagnosis		
CRC	- 0.201 [0.213]	0.3456
Crohn's disease	-	-
Baseline CRP [log]	0.097 [0.032]	0.0030
Preoperative Crohn's medication	0.173 [0.170]	0.3106
Postoperative antibiotics	0.168 [0.126]	0.1881
Age	0.002 [0.004]	0.6949

SE, standard error; CRP, C-reactive protein; CRC, colorectal cancer.

significant at Day 6 only [39% higher CRP in CD group, $p = 0.036$] [Figure 2]. Even after correction for age, pre- and postoperative intake of antibiotics or immunomodulators, and preoperative CRP level, the postoperative CRP level remained significantly higher in the CD group at Day 6 [64%, $p = 0.035$]. Multivariate regression analysis is represented in Table 2.

4. Discussion

Our series of 224 patients showed a significantly increased inflammatory response in patients operated for CD, compared with patients undergoing the same operation for CRC. CRP was significantly higher on postoperative Days 1, 4, 5, and 6. The magnitude of the average difference decreased and statistical significance disappeared on Days 1, 4, and 5 when correcting for preoperative CRP, suggesting that the baseline state of inflammation in part contributes to the postoperative response. The occurrence of an enhanced postoperative inflammatory response has been confirmed in other series.[2,3,11]

The origin of this observation may be multifactorial. Bacterial translocation to mesenteric lymph nodes is often present in CD.[2,3] This is probably facilitated by an impaired mucosal barrier, caused by mucus alteration, damaged tight junctions, and areas of cell loss at villous tips.[12] Moreover, CD patients develop intestinal bacterial overgrowth by delayed transit time or the presence of fistulas.[13,14] The combination of an altered mucosal layer with bacterial overgrowth probably facilitates bacterial translocation.

A defect in innate immunity has been described in CD patients, reflected by a decreased accumulation of neutrophils and interleukin 8 in intestinal mucosa and the skin.[15,16] Intrinsic properties in terms of transepithelial migration and impaired cellular signalling of neutrophils seem to be changed.[17] This defect in innate immunity could have an impact on the clearance of translocated bacteria, leading to higher inflammatory response.

Bacterial translocation has been identified as a risk factor for both postoperative inflammatory response and morbidity.[3,18] Translocated bacteria induce a cytokine response, which might explain the increased postoperative inflammatory response.[19,20] Morbidity in terms of septic complications and postoperative fever in patients with bacterial translocation have been reported by some studies, often without being able to isolate any bacterial agent in blood cultures.[3,21] Further research should probably focus on the impact of improved perioperative antibiotic prophylaxis on surgical complication rates in CD patients.

This study is limited by its retrospective design. However, the use of a biological parameter renders this retrospective study more robust, by relying on objective measures. Furthermore, the low specificity of CRP has been bypassed by selecting patients without any septic complications and with the same minimally invasive access, to obtain a homogeneous population. Another limitation is the difference in age between the patients with CD and CRC. The CRP response is somewhat blunted at older age but, on the other hand, adjusting for age did not influence our results.[22] We believe therefore that CRP is a good biomarker for the impact of surgery on patients' postoperative inflammatory response.

Postoperative inflammatory response is higher in CD patients compared with CRC patients, probably rendering the postoperative diagnosis of any septic complications in those patients more delicate. This may lead to an increased rate of unnecessary postoperative medical imaging or second-look surgery. A better prophylactic antibiotic use may eventually attenuate inflammatory response in CD patients.

Conflict of Interest

None.

Author Contributions

ADBVO, SVH, SV, MF, GVA, AW, and ADH were responsible for the treatment of all included patients. ADBVO, SVH, GVA, MF, SV, AW, SF, and ADH were responsible for designing the study. ADBVO and SVH were responsible for acquisition of data. SF was responsible for statistical analysis of the data. ADBVO, SVH, GVA, SV, MF, SF, AW, and ADH were responsible for interpretation of the results. ADBVO was responsible for drafting the manuscript. All authors reviewed and accepted the final version of the manuscript.

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